

REMARKS

The Office Action dated August 18, 2006, has been carefully reviewed and the foregoing remarks are made in response thereto. Applicants note that claims 32-33 have not been rejected under 35 U.S.C. § 102 or 103 and appear to be allowable, but for the pending obviousness-type double patenting rejections. In view of the following remarks, Applicants respectfully request reconsideration and allowance of the claims.

Claims 26-30, 34-36, 38-39, 42-51 and 53-54 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Drmanac et al. (EP 392 546, published October 17, 1990) in view of Ghosh et al. (Nucleic Acids Res. 15(13): 5353-72 (1987)). According to the Office Action, Drmanac teaches the use of discrete particles each containing a unique species of oligonucleotide probe having a length of 4-20 bases. The Office Action acknowledges that Drmanac does not teach the use of nucleic acids between 25-100 nucleotides in length as recited in the pending claims. However, the Office Action asserts that it would have been prima facie obvious at the time the invention was made to have modified the teachings of Drmanac with the teachings of Ghosh for using probes of 17-29 nucleotides in length because Ghosh teaches that this range “allows for screening of presence of target sequences” (Office Action, p. 5). Applicants respectfully traverse the rejection.

The skilled artisan would not have been motivated to modify the teachings of Drmanac to use probes of more than 20 nucleotides in length because Drmanac specifically teaches that probes of 20 nucleotides are the longest probes suitable for the methods disclosed therein. Further, Drmanac also teaches that the skilled artisan should stray away from probes having longer lengths to avoid uncertainty in hybridization. There would be no motivation for the skilled artisan to substitute probes having lengths longer than 20 nucleotides in the methods of Drmanac, particularly since the Drmanac reference itself cautions against using longer probes.

To understand the teachings of Drmanac, one must first appreciate that Drmanac discloses two types of hybridization reactions: (1) “direct” sequencing by hybridization or “SBH” and (2) “indirect” sequencing by hybridization or “ISBH.” In direct SBH, genomic fragments are bound to discrete particles or “DPs” and hybridized with oligonucleotide probes. In ISBH, oligonucleotide probes are bound to DPs and hybridized with genomic

fragments. When the Examiner asserts that Drmanac teaches discrete particles each containing a unique species of oligonucleotide probe having a length of 4-20 bases, the Examiner is specifically referring to the ISBH embodiment proposed by Drmanac.

At page 6 of EP 392 546, column 10, beginning at line 35, Drmanac discusses the characteristics of ISBH. As stated in section 2, one of the characteristics is:

2) A possibility for preparation of OHA of different complexity for sequencing fragments of different lengths. One can imagine OHA with 200000 9-mers for sequencing 1-2 Kb fragments, OHA with 4 million 11-mers for sequencing cosmids inserts of 50 kb, OHA with 65 million 13-mers for sequencing YAC inserts and, what is certainly most attractive, OHA with from 1 billion of 15-mers to 1000 billion of 20-mers for sequencing complete chromosomes, or genomes, or entire mRNA (cDNA) of specific tissue in only one hybridization reaction. (With emphasis.)

Thus, it is clear from this section of Drmanac that the recommended length of probe increases as the size of the target increases. It is also clear that 20-mers, which are the longest probes contemplated, would be sufficient for even the largest targets to be sequenced, i.e., chromosomes, genomes or entire mRNA.

The question becomes, then, would the skilled artisan be motivated by the cited references to use even longer probes even though such probes would not be necessary to sequence even the largest targets according to Drmanac? Applicants respectfully submit that the skilled artisan would not be motivated to use longer probes, particularly since Drmanac teaches that the skilled artisan should stray away from probes having longer lengths to avoid uncertainty in hybridization.

For instance, as stated in Drmanac on page 7, column 11 at line 36: "The main uncertainty of ISBH is hybridization with every complex probe, *especially in the case of using ONPs longer than 13 bases* and genomic fragments larger than a million bp. The basic problem is simultaneous hybridization with ONP having two extreme GC contents." (With emphasis.) Thus, according to Drmanac, uncertainties in using ISBH are greater when oligonucleotide probes are used that are longer than 13 bases. As stated at column 7, line 24, "In order to avoid forming a great number of SFs [genomic subfragments], it is necessary to have such a ratio between L [length of target] and N [length of probe] that, on average, only each tenth ONP possesses complementary sequence in the given fragment of genomic DNA." As further

explained at page 6, column 10, lines 15-22, for mammalian genomes, the most suitable length is a 17-mer. As stated therein, “On the average, each tenth 17-mer should have a complementary sequence in a given mammalian genome.”

Thus, not only does the Drmanac reference teach that a 20-mer is sufficient for even the largest targets to be sequenced, for instance a mammalian genome, the reference also cautions against using probes that are too long. In fact, Drmanac suggests that the ideal probe length for sequencing a mammalian genome is actually more on the order of 17 nucleotides rather than 20, given the uncertainties involved in using longer probes.

In light of this disclosure in Drmanac, the Office Action has provided no reasonable explanation as to why the skilled artisan would be motivated to use the longer probe lengths disclosed by Ghosh et al. The only reasoning offered in the Office Action is that the skilled artisan could use the probes of Ghosh et al. to screen for the presence of target sequences. However, the disclosure of Ghosh et al. does not concern sequencing by hybridization or arrays containing discrete particles bound to nucleotide probes. Therefore, it is difficult to see how the skilled artisan would have believed that the longer probe lengths described in Ghosh et al. would be suitable for the methods disclosed in Drmanac. As the Federal Circuit recently explained in *Alza Corp. v. Mylan Labs., Inc.*, No. 06-1019, 2006 U.S. App. LEXIS 22616 (Fed. Cir. Sept. 6, 2006), “the suggestion test—as our motivation-to-combine inquiry has come to be known—‘prevent[s] statutorily proscribed hindsight reasoning when determining the obviousness of an invention.’” *Id.* at *7.

According to the Board (*Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)):

To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.

Similarly, the Federal Circuit has set out a test for combining references. In *Dystar v. Patrick*, 464 F.3d 1356, 1360 (Fed. Cir. 2006), the Court stated:

Where, as here, all claim limitations are found in a number of prior art references, the factfinder must determine "[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references". *In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Here, the prior art certainly fails to suggest the desirability of the combination given that Drmanac actually teaches away from using longer probes. The Federal Circuit has made it clear that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Furthermore, if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Similarly, in the instant situation it appears that the use of longer probes as disclosed in Ghosh et al. could even render the methods of Drmanac unsatisfactory due to the uncertainties in hybridization introduced by the substituting longer probes.

In view of the above remarks, reconsideration and withdrawal of the rejection of claims 26-30, 34-36, 38-39, 42-51 and 53-54 under 35 U.S.C. § 103(a) are respectfully requested.

Claims 26-28, 30, 34-38, 40-49, 51-53 and 55 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Southern (WO 89/10977) in view of Ghosh et al. (Nucleic Acids Res. 15(13): 5353-72 (1987)). According to the Office Action, Southern does not specifically teach using beads for the point mutation analysis nor does it specifically teach using nucleic acids between 25-100 nucleotides in length. However, the Office Action asserts that Southern allegedly teaches oligonucleotide synthesis upon a solid support of controlled pore size glass and suggests that oligonucleotides might be used as probes while still attached to the matrix, and that it would have been obvious to use the

beads of Ghosh et al. that contain probes having 20-50 nucleotides in the methods of Southern. Applicants respectfully traverse the rejection.

Applicants fail to see how the combined references teach or suggest every limitation of the claimed invention, since for instance, neither of the cited references teaches a method as claimed including but not limited to limitations directed to a set of at least 100 beads as claimed or that the beads are coded with an encoding system whereby the target specific sequence of each probe nucleic acid attached to the beads can be identified. For instance, as addressed by the Examiner, Southern merely teaches synthesis on columns of controlled pore size glass (CPG). As apparent to one of skilled in the art, this teaching in Southern merely refers to the column matrix upon which single species of oligonucleotides are synthesized (p.12). As such, each particle of the CPG matrix in a column comprises the same sequence. Accordingly, Southern does not teach nor suggest a set of 100 beads as claimed, i.e., where each of the 100 comprise a different probe sequence, let alone an encoding system on each bead. Respectfully, Gosh does not cure this deficiency. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The Examiner has not shown where either Southern or Ghosh teach the use of beads being coded with an encoding system as recited in the current claims.

In view of the above remarks, reconsideration and withdrawal of the rejection of claims 26-28, 30, 34-38, 40-49, 51-53 and 55 under 35 U.S.C. § 103(a) are respectfully requested.

Applicants acknowledge the obviousness type double patenting rejections set forth on pages 9-12 of the Office Action. While not agreeing with the rejections, Applicants respectfully request that they be held in abeyance until the determination of otherwise allowable subject matter at which time Applicants will consider submitting a terminal disclaimer.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicant respectfully requests entry of the amendments, reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1283. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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